All contributions to be sent to the Editor, 19 St. Andrew's Mansions, Dorset Street, W.1. (Telephone, Welbeck 9631.)

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CELLULAR RESPIRATION

BY

L. CORSAN REID, M.D., NEW YORK

CELLULAR respiration may be defined as those biological processes and chemical mechanisms by which the cell converts the bound, radiant energy of the sun, stored in foodstuff molecules, to free utilizable biotic energy, thereby making possible cellular activity and even cellular existence.

It is becoming increasingly obvious that this essential link in the chain of events, going under the general term of respiration, has not received from the clinician in general, or the anæsthetist in particular, the attention its fundamental importance would seem to warrant.

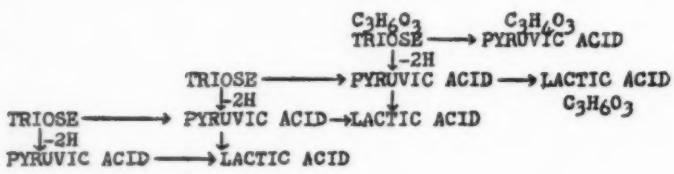
In order to give a reasonably complete picture of the present status of this subject it may be necessary at times to treat it in a rather arbitrary fashion, or indeed, to oversimplify the mechanisms concerned, but in any event, all present conceptions must be considered as being more or less on probation. In extenuation of being too precise or too dogmatic about so many unsettled questions, one might quote Macaulay's famous remark, "Bad generals have won battles, but a debating society never did." The cell, according to Szent Gyorgyi,[1] has two methods for liberating the energy present in the foodstuff molecules: (1), fermentation; (2), oxidation.

Fermentation.

Fermentation is the term used to cover those processes by which glucose is converted into simpler substances in the absence of oxygen with the liberation of energy. In the case

of the yeast cell, this is represented by a conversion of glucose to ethyl alcohol; in that of the muscle cell, the conversion of glucose to lactic acid. These two processes have more in common than might appear at first sight, as alcohol represents merely a modified lactic acid. Fermentation is a phylogenetically older biological mechanism than oxidation. The process is relatively simple, the presence of oxygen is not necessary; it is very wasteful, and is capable of supporting only the simplest forms of life. The essential steps in fermentation, according to the work of Dische, Meyerhof, and Parnas as quoted by Szent Gyorgyi,[2] consists in the splitting of the glucose molecule into two molecules of triose, which are then converted to pyruvic acid, which in turn are reduced to lactic acid. These represent the main or essential steps, but omit certain details such as it starting out with a triose phosphoric acid compound and going through a pyruvic phosphoric acid substance to lactic acid. Phosphorus has a very important role, and acts as a sort of vehicle to transport the energy from one step to the next. These steps are made possible by the organic catalysts or enzymes known as dehydrogenases and may be diagrammatically represented as follows, as taken from Szent Gyorgyi.[3]

The arrows represent dehydrogenases.



Oxidation.

Oxidation is a term used to cover those processes by which glucose is converted into simpler substances in the presence of oxygen with the liberation of energy. In the case of the muscle cell, for example, the process consists in the conversation of glucose to carbon dioxide and water.

In the evolution of life from lower to higher forms, a more efficient mechanism for liberating the energy in the foodstuff molecules was a concomitant development and this resulted in the setting free of thirty times more energy than occurred with

fermentation alone. It has been known since the time of Pasteur that these two processes were interdependent, and when oxygen was lacking fermentation was the energy-producing activity, while in the presence of oxygen, oxidation was the mechanism in operation. Before proceeding further, one must clearly understand that oxidation can take place by three different operations:

1. Addition of oxygen.
2. Removal of hydrogen.
3. Loss of an electron.

and reduction means:

1. Removal of oxygen.
2. Addition of hydrogen.
3. Addition of an electron.

The elucidation of the essential steps in oxidation reveal it to be a much more complicated process than fermentation. It was due to the work of Szent Gyorgyi[4] and his co-workers that the primary substance from which those processes peculiar to oxidation started was found to be a triose compound; the same as that met with in fermentation. The main steps in this process, therefore, are a transference by the enzyme, dehydrogenase, of 2H atoms from triose to oxaloacetic acid, which is then converted to malic acid, then through the intermediation of the enzyme, fumarase, 2H atoms are transferred from malic acid to fumaric acid, which is then converted to succinic acid. The enzyme, succino dehydrogenase, transfers the 2H atoms to oxidized cytochrome which then becomes reduced. This reduced cytochrome has its 2H atoms removed through the action of the enzyme, oxidase, in the presence of molecular oxygen to again form oxidized cytochrome and water which disappears from the cycle. The oxidized cytochrome is then available to take 2H atoms from succinic acid which then becomes fumaric acid, which is then available to take 2H atoms from malic acid, which then becomes oxaloacetic acid, which in turn is ready to take 2H atoms from the triose and so on round the cycle again. See Fig. 1 for diagrammatic details of the oxidation cycle.

Szent Gyorgyi[5] has illustrated in a very brilliant and con-

vincing fashion these chemical events and the relationship between fermentation and oxidation, as well as how the simpler evolved into the more complex mechanism. He has done this by placing the formulae of one group of reactions above the other, and as he says, one of the most amazing implications of this theory is that hydrogen represents the essential fuel of the cell, and that oxygen plays a relatively subsidiary role, disappearing early in the proceedings to form water. See Fig. 2 for a diagrammatic representation of fermentation and oxidation and their interrelationship.

The various elements entering into these processes warrant a little more detailed consideration.

Glycogenolysis.

This represents the conversion of glycogen to glucose and, strictly speaking, does not form a part of cellular respiration, but is added for the purpose of rounding out the picture with some degree of continuity and completeness. This process occurs through the intermediation of about ten different enzymes (Green[6]) including phosphatases, phosphorylases, mutases, etc. Besides these enzymes, the nucleotide, adenylic acid, plays a highly important role.

Enzymes.

It is well known that hydrogen and oxygen do not combine with a measurable velocity at ordinary temperatures but will do so under special conditions, such as the presence of inorganic catalysts, for example, palladium or platinum or enzymes so-called organic catalysts.

Dehydrogenases.

The enzymes, dehydrogenases were first described by Wieland and have since been extensively investigated by Thunberg,[7] who has recently published an extensive review. These dehydrogenases are responsible for the activation of the hydrogen of the foodstuff molecules, which is transferred to a suitable acceptor or carrier substance. They are highly specific in their actions, that is, some will only transfer hydrogen to cytochrome, others to flavoprotein, and it is interesting in this connection to note

that this specificity is due to the variability of the bearer portion of the molecule. Their prosthetic groups are all the same. The peculiar specificity of reaction depending on changes in the bearer portion rather than the active prosthetic group seems, at first sight, to be unusual, but the well-known substance, hæmoglobin, is an example of a similar action.

For example, the hæmoglobin of the fœtus has a much greater affinity for oxygen than maternal hæmoglobin, Hill[8]. The hæmoglobin of the muscle has a higher affinity for oxygen than the hæmoglobin of blood. The hæmoglobin of muscle according to Millikan[9] loses carbon monoxide ten times as rapidly as blood hæmoglobin, although their affinities are about the same. This variability of action on the part of hæmoglobin is dependent on a difference in the globin portion as the hæm molecules are identical. Theorrel[10] has shown that muscle hæmoglobin has a molecular weight of 34,000, just half that of blood hæmoglobin, and Millikan[11] has recently further revised this figure to 17,200. This illustration of the variability of hæmoglobin activities without any changes in the prosthetic or active group is particularly useful in understanding the specificity of enzyme reaction and their almost endless variety.

Fumarase.

Fumarase is a very powerful enzyme present in all tissues, having the unique quality of maintaining the ratio of malic acid to fumaric acid in the proportion of three to one.

Oxidase.

The enzyme, oxidase—or as it is sometimes called, the respiratory enzyme, or the Atmungsferment of Warburg—is unusually widely distributed and has apparently a specific relationship to reduced cytochrome to activate its hydrogen, and in the presence of molecular oxygen to form water.

Four Carbon Dicarboxylic Acids.

The role of the four carbon dicarboxylic acids are very important. These are unique substances. It is a simple rule of biological chemistry that the first and second molecules next the COOH group are the most reactive, and, therefore, these sub-

stances having the central CH_2 groups in both the alpha and beta position possess unusual chemical affinities, and as Szent Gyorgyi says, gives these substances their peculiar reactivity.

Respiratory Carriers.

Respiratory carriers are substances which can be hydrogen acceptors and, under certain conditions, hydrogen donators. These play an essential role in all oxidation reduction systems. The better known ones are:

1. Cytochrome.
2. Flavoprotein.
3. Coenzyme I.
4. Coenzyme II.
5. Glutathione.

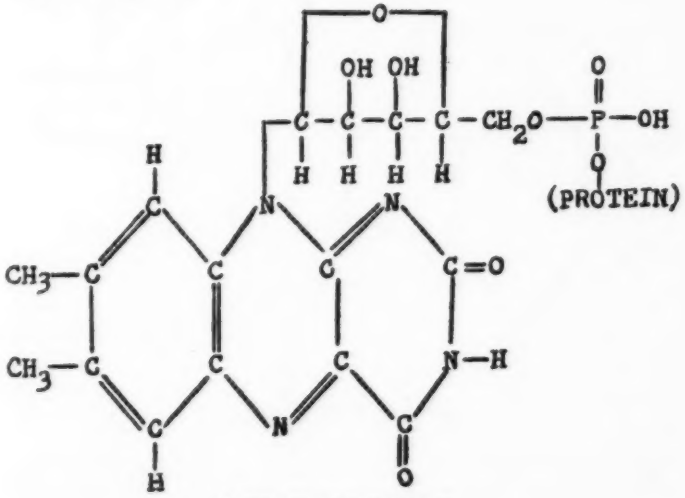
A few remarks about these substances should serve to clarify their actions.

Cytochrome.

Cytochrome is the name of a widely distributed cellular pigment originally discovered by MacMunn in 1887 at Cambridge, but his work received such severe criticism from Hoppe Seyler and his pupil, Levy, that it never received the attention its importance warranted. The substance was rediscovered by Keilin [12] in 1925 who gave it the present name. Cytochrome is a mixture of three hæmochromogen compounds, hæmochromogen being a combination of a hæmatin and a nitrogenous base like nicotine or pyridine.

Cytochrome is unusually abundant in vertebrate hearts and yeast. There is a definite parallelism between the amount of this substance present in any tissue and its respiratory activity. For instance, in crabs and frogs, it is mostly in the heart with very little in the legs (Barcroft [13]). In birds, it is found mostly in the pectoral muscles and the heart. In those insects whose wings have a 300 times per second movement the wing muscles contain the highest percentage of cytochrome. In cockroaches, which are good runners but do not fly, cytochrome is found mostly in the leg muscles. In the moth, the male has fully developed wings with much cytochrome, while the female has

poorly developed wings and no cytochrome. If one takes a thick suspension of yeast in a test-tube and examine it with a microspectroscope the lines of reduced cytochrome are present. On shaking with air these lines disappear due to the oxidation of the cytochrome and the changing of the FeO, ferrous iron, to Fe_2O_3, ferric iron. Cytochrome does not lose its oxygen in a vacuum like hæmoglobin. The heart, according to Keilin and Hartree,[14] in mammals is the best source of cytochrome. Cytochrome goes through an oxidation reduction cycle 3,000 times per minute *in vivo*, while *in vitro* this is reduced to about 300 times (Green[15]).



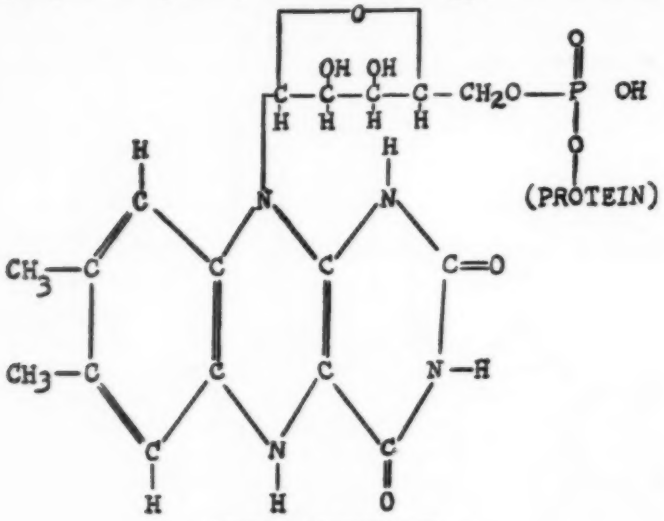
OXIDIZED FLAVOPROTEIN.

Flavoprotein.

Flavoprotein is another widely distributed pigment, and is also known as the yellow enzyme of Warburg. The prosthetic group of this enzyme was discovered by Szent Gyorgyi, who called it cytoflav, but its actual structure was worked out by Warburg.[16]

When this cytoflav is joined through the sugar, d-Ribose, and phosphoric acid to a protein, it becomes flavoprotein. This

is a hydrogen carrier, but differs from cytochrome in containing no iron. It bears a very specific relationship to certain dehydrogenases, and under some conditions it joins the chain as a second carrier to cytochrome. In this connection it is interesting to note that the riboflavin portion of vitamin B_2, or as it is sometimes called, vitamin G, has a formula identical with the prosthetic group of flavoprotein, and it has been suggested that the dis-

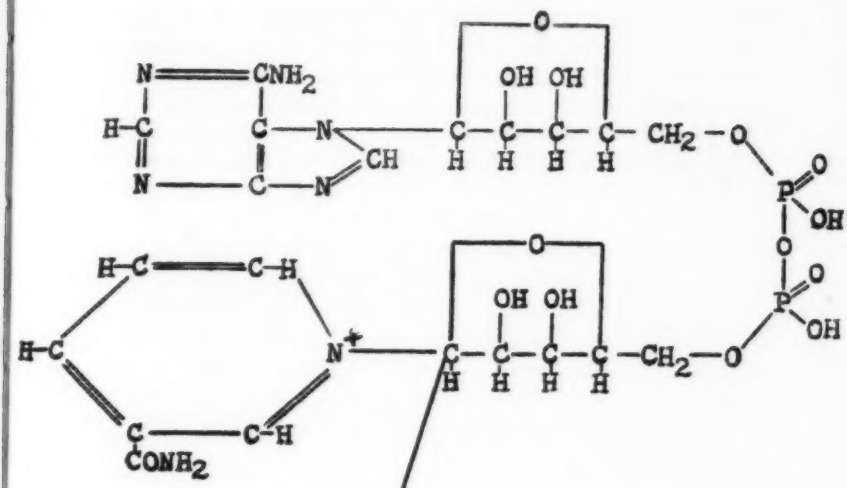


REDUCED FLAVOPROTEIN.

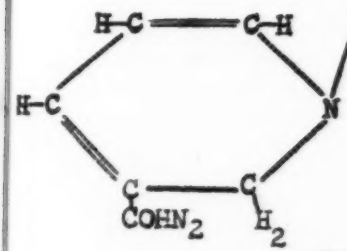
turbances of vitamin B_2 deficiency can be explained by a lack of flavoprotein, and as a result, a decreased efficiency in cellular oxidation reduction systems. This substance carries its hydrogen atoms attached to N, which on oxidation is replaced by double bonds.

Coenzymes I and II.

It has been known for some years that some dehydrogenases could only reduce particular dyes in the presence of certain specific cellular constituents which received the name of coenzymes. However, as a result of the work of Warburg and his group, these coenzymes have been found to be true carriers



OXIDIZED COENZYME I



The oxidized Coenzyme I has one less hydrogen atom and one less electron than the reduced Coenzyme I.

REDUCED COENZYME I.

and play an important part in the transfer of hydrogen to flavoprotein. According to Szent Gyorgyi[17] their role as respiratory carriers with the action of the dehydrogenases account for the changes occurring in the four carbon dicarboxylic acids. This transference is accompanied through their nicotinic acid amide ring.

In the case of coenzyme II there are $3H_3PO_4$ groups uniting

the ribose sugars, and this is the only difference. This nicotinic acid amide, therefore, represents an important part of coenzyme structure, and as nicotinic acid is the pelagra preventing portion of vitamin B_2 its deficiency must necessarily curtail the coenzyme formation with a resulting loss of efficiency in an essential constituent of cellular oxidation reduction systems.

Glutathione.

Glutathione, discovered by Hopkins[18] in 1921, represents one of the earliest carriers found, and at first was considered to play a dominant role in oxidation reduction systems. However, its exact position is not evident, and in any event it seems to be decreasing in importance. Another respiratory carrier is the recently discovered adrenochrome (Green and Richter[19]), but at the moment its exact significance in the scheme of things is not at all clear.

The Effects of Various Substances and Conditions on Cellular Oxidation Reduction Systems.

The accumulation of local tissue metabolites and elevation of temperature accelerates the reduction of cytochrome (Keilin[20]). If cyanides, sulphides or nitrites are added to this oxidation reduction system all respiration ceases, but there is no change in the spectrum of cytochrome, therefore some other part of the chain must be involved. This has been found to be the respiratory ferment, oxidase. Of course, interference with any link in the chain arrests the whole process. Therefore, drugs of the type of cyanides, sulphides, and nitrites have their effects on cellular respiration restricted to the one link of the enzyme, oxidase. The alkaloids, and probably most anæsthetic agents, have their actions on the other end of the chain and involve the enzymes, dehydrogenases. The characteristic action of iodo-acetate on the muscle is due to its action on the dehydrogenases, particularly in the transition of triose to pyruvic acid (Dixon[21]).

Comment.

An important question arises as to how one is going to utilize practically these conceptions of cellular oxidation reduction sys-

tems. To the clinician it becomes a matter of importance as to the dietary regime, especially regarding vitamin B_2 content during the course of any condition in which these mechanisms are under strain. For instance, in conditions such as decreased blood volume, anæmias, cardiac or pulmonary diseases, etc. To the anæsthetist who by the use of anæsthetic agents inhibits the efficiency of these mechanisms, the diet preoperatively becomes of even greater importance, and one can readily understand that without adequate vitamin B_2 there cannot be a sufficiency of respiratory carriers like flavoprotein or the coenzymes because the material necessary for their synthesis would not be available. Previously, failures in oxidative processes due to this factor have been explained in terms of circulatory disturbances, low hæmoglobin, etc.

The post-operative supplemental supply of oxygen becomes a very logical procedure in the light of this scheme, and under many conditions an imperative necessity. For example, it is well known that in high mountain altitudes the decreased oxygen tension is compensated for by increased blood volume, increased red cell count, increased percentage of hæmoglobin, and increased respiratory activity. Therefore, it would seem a perfectly logical procedure to compensate for a decreased efficiency of cellular oxidation reduction systems as a result of anæsthetic agents by an increased oxygen tension through a supplemental oxygen supply. This, of course, is most important in the immediate post-operative period although it is still of value whenever the cellular oxidation reduction systems are under strain as in anæsthesias, anæmias, shock, etc. This would seem to provide an excellent basis for the wider application of the use of a post-operative supplemental oxygen supply.

If one speculates on this scheme, some otherwise imperfectly understood phenomena become more susceptible of understanding. For example, it is well known that anæsthetic agents such as ether, etc., give rise to a pronounced hyperglycæmia which is not fundamentally an autonomic nervous system effect as it is uninfluenced by adrenalectomy, atropine, or ergotoxine (MacIntosh and Pratt[22]). The genesis of this hyperglycæmia is, therefore, not clear, but if one considers that these anæsthetic agents inhibit the dehydrogenases with a consequent decreased tissue utilization of triose and its parent, glucose, which accumu-

lates in the blood particularly if the enzymes responsible for the conversion of glycogen to glucose are not inhibited, then a ready explanation is available. Another interesting phenomenon is that of the use of morphine in cyanosis and dyspnœa. It is well known that morphine is very beneficial in cases with cyanosis and dyspnœa as a result of cardiac decompensation, but on the other hand was positively harmful when these symptoms were due to pulmonary lesions such as bronchitis, emphysema, asthma, etc. The explanation given has been entirely founded on the depression of the respiratory centre, but if this were the whole story an accumulated CO_2 should stimulate even a depressed centre. Therefore, if one turns to this scheme it shows at once that morphine, being an alkaloid, depresses the dehydrogenases, the cellular use of oxygen is inhibited, less carbon dioxide is formed, and eventually less chemical stimulation of the respiratory centre takes place from accumulated carbon dioxide. Therefore, in severe inhibition of the dehydrogenases the respiratory centre is only stimulated by the action of oxygen deficiency on the specific nerve endings in the aorta. This, of course, gives a shallow gasping respiration which is not efficient enough under such conditions, and that respiration sometimes abruptly fails is not surprising. Not infrequently, in other cases of a lack of carbon dioxide build up where the classical explanation has been the insufficiency of oxygen intake, an inhibition of the dehydrogenases probably plays a very important role.

Summary.

A scheme has been presented showing:

1. The main steps in the mechanism for the cellular use of oxygen and the liberation of the energy in the foodstuff molecules.

2. The high value of an adequate oxygen supply during anæsthesia as well as the utilization of a supplemental oxygen supply in post-operative period.

3. The alkaloids and probably most anæsthetic agents act on the dehydrogenases. The cyanides and sulphides, etc., act on the oxidases.

4. An adequate vitamin diet, particularly vitamin B_2, is of the utmost importance whenever this cellular oxidation reduction mechanism is, or is about to be, placed under strain.

FIG. 1.
OXALO ACETIC ACID
MALIC ACID
FUMARIC ACID
SUCCINIC ACID
Under action of dehydrogenases in the presence of a coenzyme these 2H atoms reduce
which forms
then the enzyme fumarase transfers 2H atoms to
which is reduced to
Next the succino dehydrogenase transfers 2H atoms to
OXIDIZED CYTOCHROME
which is changed to
REDUCED CYTOCHROME
Under action of enzyme oxidase in presence of molecular oxygen the 2H atoms are added to the oxygen to form water which disappears from the cycle and leaves oxidised cytochrome.
H_2O
TRIOSE
MALIC ACID which becomes oxalo acetic acid
2H
FUMARIC ACID which oxidizes malic acid
SUCCINIC ACID then becomes fumaric acid
2H
OXIDIZED CYTOCHROME oxidizes succinic acid
The remainder of the triose molecule with addition of water is broken up through various stages to carbon dioxide and hydrogen, the 2H atoms going along this cycle and the carbon dioxide being removed by the blood, and carried to the lungs, where it is given off

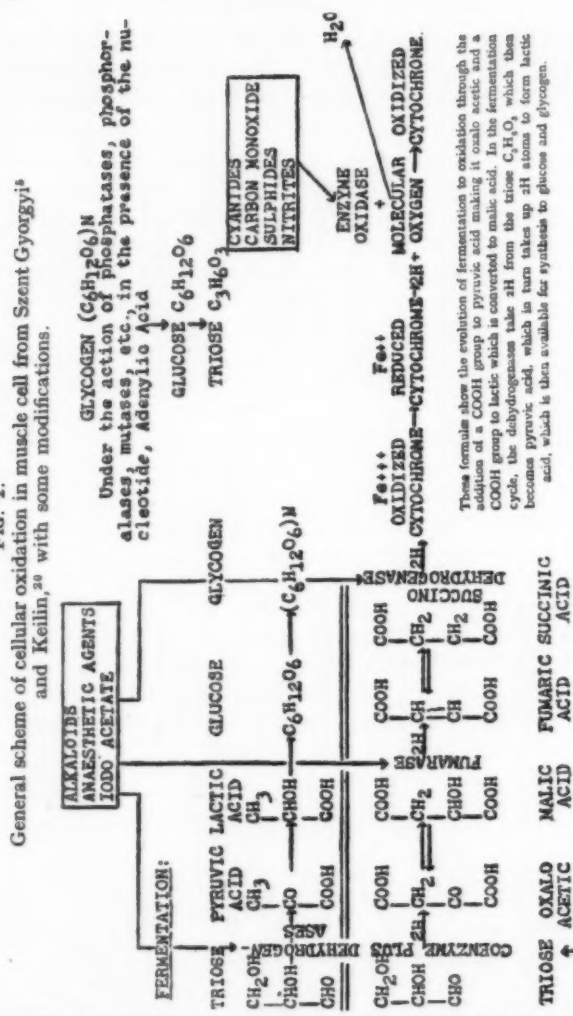
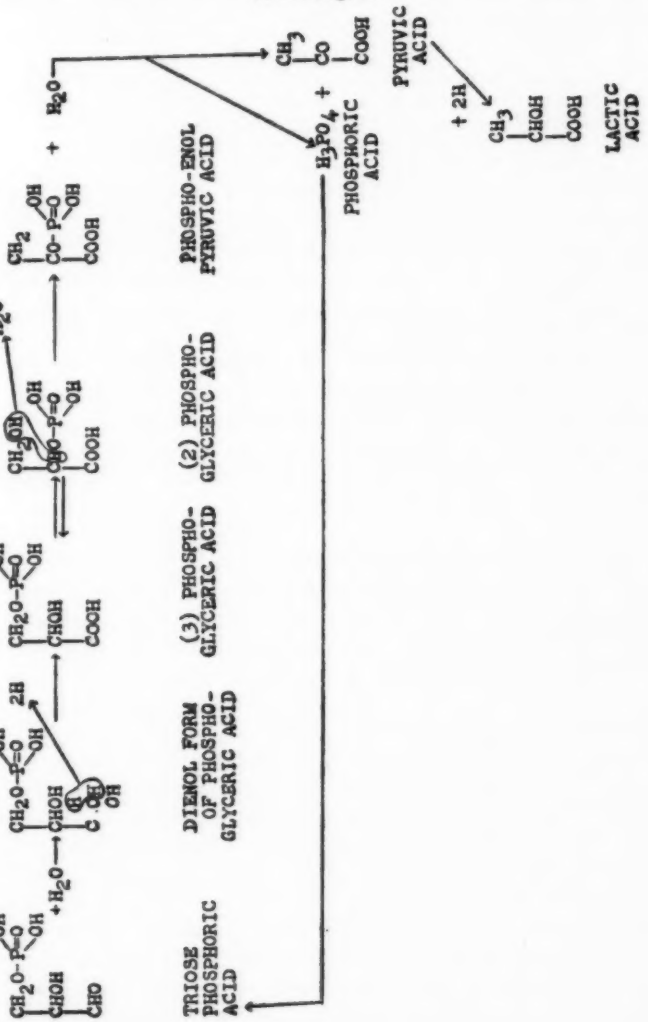


FIG. 2.
General scheme of cellular oxidation in muscle cell from Szent Gyorgyi[3] and Keilin,[20] with some modifications.

In this scheme the upper part represents fermentation and the lower oxidation. Due to the action of the dehydrogenases in association with a coenzyme or codehydrogenase, the hydrogen of the triose is mobilized and transferred to oxalo acetic acid, which then becomes malic acid. The 2H atoms are transferred from malic acid under the influence of the enzyme fumarase to fumaric acid, which then becomes succinic acid, which in turn, under the influence of succino dehydrogenase, gives up 2H to oxidized cytochrome, which then becomes reduced cytochrome. These 2H are then removed by the enzyme, oxidase, in the presence of molecular oxygen to form water, which disappears from the cycle, leaving oxidized cytochrome, which is then available to take 2H atoms from succinic acid and so on round the cycle again.

FIG. 3.

This scheme illustrates the intermediate steps in the transition of triose to pyruvic acid—for example, in muscle cells—and gives an objective picture of what is meant by saying some of the details have been left out of Fig. 2.



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THE TEACHING OF ANÆSTHETIC METHODS FOR USE IN GENERAL PRACTICE

BY

JOHN ELAM, B.A., M.R.C.S., L.R.C.P.

PATIENTS who go to a general practitioner for advice need the assistance of a man or woman of practical ability who can see them through their difficulties. They do not need, as a rule, the assistance of a professor of anatomy or physiology, and it is essential that before being sent out into the world general practitioners should have a good working knowledge of the subjects which they will be required to practise. There is nothing more important both to the general practitioners and their patients than that they should have a sound working knowledge of anæsthesia, and I submit that there is very urgent need for improvement in the teaching of anæsthesia. It is manifestly absurd that a practitioner having no knowledge of anæsthesia can be " licensed to kill ".

Students should first of all be taught that there is such a thing as the science of anæsthesia, and that they cannot easily become masters of this science. They must be made to understand that to become accomplished anæsthetists a high degree of skill must be attained and that this degree of skill can only be acquired by long experience and practice.

After many years experience as a general practitioner anæsthetist I am convinced that a great gulf separates the genuine specialist anæsthetist from the amateur, or general practitioner anæsthetist, however gifted the latter may be. This gulf cannot be crossed, and students should be taught early in their career that their first duty is to the patient, and that they must not attempt to deal with cases which are not within their province. Practitioners should be as ready to call in the specialist anæsthetist as they are to seek the assistance of other specialists.

It is a matter of great regret that, while genuine professional surgeons on the staffs of teaching hospitals are now usually

appointed to the staffs of smaller provincial hospitals, both voluntary and rate-supported, it is a matter of extreme rarity to find professional anæsthetists so appointed.

No time should be lost in remedying this defect. Thus could the surgeon always be sure of obtaining adequate anæsthesia for a difficult case and the general practitioner obtain advice and guidance in his own anæsthetic practice. The first step towards happier conditions is to raise the status of anæsthesia. Anæsthesia must be recognized for what it is, a brand of medicine of equal importance to ophthalmology, oto-rhinology, dermatology, or general surgery.

The course of study of anæsthesia in the medical curriculum should last at least three months, and special attention should be paid to dental work. The student should be required to produce evidence that he is a capable dental anæsthetist.

The importance of dental anæsthesia is stressed because all general practitioners have to give anæsthetics for dental extractions, and, too often finding a dental nasal gas beyond their capabilities, they turn readily to the use of intravenous anæsthesia, which requires much practice and experience for really safe administration.

Anæsthesia and analgesia in midwifery probably come next in importance in general practice, and special attention should be given to teaching students both the value and the dangers of relieving the pains of labour by the use of anæsthetic agents.

In general surgery the general practitioner anæsthetist requires to know two things:

1. Some practical and safe method of premedication.
2. A not too complicated method of administration of inhalation anæsthesia.

Students should be taught the importance and value of premedication, and should learn in hospital methods of premedication which are appropriate to general practice. It is no use talking to most of us about avertin. Avertin is a perfect nuisance in general practice. We have got our morning surgeries to do, and we cannot run up to the hospital or nursing home first thing in the morning and administer avertin, and even if we can manage this we probably find there has been some delay in its arrival.

What we really do need is some safe, reliable sedative drug

which can be given by mouth, which will not depress the patient's respiration too much and from which the patient will recover in reasonable time.

I have found "Seconal"* the most satisfactory drug for premedication up to the present.

I give three capsules by mouth to a normal adult, and I find that in 90 per cent. of cases the patient comes to the theatre really sound asleep and that the normal progress of the anæsthetic is not interfered with. In about 5 per cent. of cases I get no results at all, simply because it is not given, forgotten, or else the sisters do not like it. The remaining 5 per cent. of patients are drowsy but not sound asleep. I have noticed, too, there is a very marked reduction in post-anæsthetic vomiting after Seconal has been administered. In a series of one hundred consecutive cases, vomiting only occurred in twenty-four, in no case did the patient vomit more than three times, and in no case did vomiting persist more than eight hours after the completion of the operation. Other practitioners may have other and possibly more satisfactory drugs to use for premedication, but it is essential that the young practitioner on leaving hospital should be thoroughly familiar with all practical methods of allaying the patient's anxiety before the operation.

For the actual performance of the operation the student should become thoroughly familiar with the administration of open ether, special attention being given to the induction of the anæsthetic. This can be done by allowing the student to administer open ether in hospital to all those cases for which this method is suitable.

It has been disappointing to me to find how seldom Vinesthene-Ether mixture is used in our teaching hospitals.

Open Vinesthene-Ether appears to me to be the ideal anæsthetic for the general practitioner. It is made up in 8-oz bottles of a very convenient size, into which the ordinary ether dropper-cork just fits. All the anæsthetist has to do is simply to drop the mixture straight from the bottle slowly on to an open mask, increasing the drop as the patient becomes accustomed to the mixture.

Full anæsthesia with excellent relaxation is usually obtained

* "Seconal". Eli Lilly & Co., Basingstoke, Hants.

in a very short time, and although occasionally coughing and straining may arise this is usually only with the very strong muscular patient.

For the more difficult cases, where, for example, endotracheal anæsthesia is required, the student can study the technique of the visiting anæsthetist until he is himself capable of using such a method.

If a three months' course of instruction in anæsthetics is established, the student should have an opportunity of becoming competent to adopt endotracheal methods.

It will naturally be asked:

1. Is there any need for the more thorough instruction of students in anæsthesia?
2. Can this instruction be given without unduly lengthening an already too long course of study?

The need for a more thorough instruction of students in anæsthesia can be estimated from the fact that there has been a steady increase in deaths on the operating table and from the constant complaints of surgeons and dental surgeons as to the inefficient anæsthetics administered for them by general practitioners.

A three months' course of instruction in anæsthesia can easily be given to medical students by cutting down the time spent on matters of purely academic interest.

THE DIPLOMA IN ANÆSTHETICS

Following the November (1939) examination the Diploma has been granted to: R. D. N. Bisset, F. K. Boston, Dorothy M. Braddock, L. G. Braddon, Elizabeth M. Corbin, T. F. Crowley, Charlotte S. Dafoe, E. W. Dunkley, G. H. Ellis, F. G. Ethirag, Margaret Forbes, P. G. Fox, Hunter Gillies, Philip Glazer, C. H. Hayes, A. L. St. A. McClosky, W. M. Maidlow, Beryl W. Mason, B. M. Phillips, T. B. Pitts, N. F. Sahor, R. N. Sinclair, and B. N. Sircar.

NOTICE

Back Numbers of the British Journal of Anæsthesia

The following back numbers of the Journal are required:

Volumes I and II.
Volume III, Parts 1, 2, and 3.
Volume IV, Parts 2 and 4.
Volume V, Part 3.
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PREVENTION OF IGNITION OF ANÆSTHETIC GASES BY STATIC SPARK

PHILIP D. WOODBRIDGE, M.D., J. WARREN HORTON, Sc.D. and KARL CONNELL, M.D.

In the Journal of the American Medical Association, August 26, 1939, Vol. CXIII, pp. 740–744.

AS a result of our investigation of a fatal anæsthetic explosion, a means of preventing ignition of anæsthetic gases by static spark has been devised which we believe to be of sufficient value to warrant general adoption.

Conditions were set up which duplicated those existing at the time of the explosion, and various observations were made. Even in the presence of 65 per cent. relative humidity, sparks were obtained. An anæsthetist wearing cotton garments acquired a potential of several hundred volts merely by sliding forward on the [rubber] cushioned stool and then rising. When woollen clothes were worn, the potential was considerably greater.

The conclusions follow:

1. Adequate protection against electrostatic sparks is not necessarily obtained by relative humidity as high as 60 per cent.
2. Cushions on the anæsthetist's stool should not be permitted.
3. If metallic electrical connection is to be maintained between the patient and the gas machine, the conductor should be placed at a distance from the breathing tubes and mask. It must be so arranged that it need never be disconnected while explosive gases are present.
4. Woollen blankets and silk woollen outer garments should never be allowed near the explosive gases. Undergarments of either silk or wool do not constitute an electrical hazard.
5. If the patient, the gas machine, [the operating table,] and the anæsthetist are so intercoupled electrically that sparks cannot occur between them, the major portion of all electrostatic potentials having dangerous possibilities is eliminated.

There are two objections to electrical intercoupling when made by conductors of high conductivity, such as wire. One is the increased hazard from electrical shock. A patient forming part of such an intercoupling system suffers a greater chance of being grounded and hence runs a greater risk of injury from accidental contact with defective electrical equipment. Second, such an intercoupled group has greater electrostatic capacity than any one of its component bodies alone. This results in a more intense spark from any charged body that may make contact with the group. These two objections may be overcome by making the connectors of high resistance, so arranged that the resistance between any two bodies in the intercoupled group is 1 megohm (1,000,000 ohms). [When such intercoupling is used,] any potential which may be established will be reduced 1 per cent. of its value in one one-thousandth second. Therefore electrostatic sparks between connected objects will be adequately prevented.

If the floor of the operating room is electrically conductive, it should be included in the intercoupled group. Then persons with conductive shoes and many other objects in the room will automatically join the intercoupled group through the medium of the floor. Similarly, connection to ground will bring all grounded bodies to the same potential as the intercoupled. Such grounding must be made through high resistance, [and] furnishes considerable additional protection against static spark.

A unit to maintain the desired interconnection has been made available. It may be attached to the operating table and [its] three wires run to the gas machine, the patient and the anæsthetist, [or] it may be attached to the gas machine and the wires run to the table, patient, and anæsthetist. Contact with a conductive floor may be made from a fifth terminal.

In the absence of such mechanical means of intercoupling, connection frequently exists through contact of the anæsthetist's hands with the gas machine and with the patient. However, any interruption, even though extremely brief, in the contact would introduce the possibility of a spark when contact is re-established. Such practice is too dependent on unremitting vigilance to be recommended.

Whatever method of intercoupling is used, all connections should be made before anæsthesia is started and maintained

until after the mask has been removed at the end of anæsthesia and explosive gases have been flushed out of the machine and the patient. Any unintercoupled person or object must not be allowed near the regions of possible escape of explosive gas (mask, breathing tubes or escape valves) without first making contact with one of the group at a point remote from such regions.

The use of high resistance intercoupling in no way eliminates the need for other precautions against static spark. High relative humidity is an additional, though unreliable, means of intercoupling. The carbon-dioxide absorption method offers two distinct safeguards: gases are not constantly blown out into the room to come in contact with various sources of ignition, and the moisture within the apparatus furnishes protection against internal spark. Rubber parts should be wet before they are used. Cloth covers should not be used on gas machines. To disconnect any portion of the breathing apparatus while it contains explosive gas is to invite danger, which is reduced but probably not eliminated by intercoupling. The unnecessary and extremely dangerous habit of removing the breathing bag during anæsthesia is probably responsible for more than one of the recent fatal explosions. If the bag hangs from the machine by a metal-to-metal slip joint, the two pieces of metal should be chained or wired together.

Ether, vinyl ether and ethyl chloride form highly explosive mixtures in air, in oxygen and in nitrous oxide. Flushing inflammable gases from the machine with oxygen is extremely hazardous. Nitrous oxide supports combustion as does oxygen. A brief flushing of the patient and the machine with a non-explosive mixture does not render conditions safe for the use of the cautery on the lung, head or neck. Machines are still commonly produced through which gases may pass under high pressure from one tank into another. Electrical apparatus used in operating rooms is often astoundingly defective in design and in maintenance.

The majority of [recent] explosions presumably initiated by static spark would have been prevented by [high resistance] intercoupling.

MEANS OF DECREASING THE TOXICITY AND COMPLICATIONS OF ANÆSTHESIA*

BY

K. E. MADAN, M.D., D.A., D.O.M.S.

Lecturer in Anæsthetics, King Edward Medical College, Lahore.

THE toxicity of anæsthetic agents depends upon various factors, viz. the quality of the drug, method of storing, method and quantity in which they are administered, the state of the patient's health, the presence of intercurrent complications, the nature of preliminary preparation and premedication, the duration of operation, and the means employed for elimination of the drug.

As regards the preliminary treatment, the *patient should be made as fit as possible to undergo the anæsthesia.* In accident cases where shock is present, and in cases where shock is anticipated, preliminary intravenous glucose saline is given, with insulin 1 unit for every 4 to 5 grammes of glucose. Insulin is useful in assisting the oxidation of glucose. In cases where much hæmorrhage has occurred or much oozing is expected during operation, as in brain surgery, transfusion of blood by the continuous-drip method is useful. In cases where lipoid soluble anæsthetics like chloroform ether or cyclopropane are to be administered, it is necessary to maintain the alkali reserve of the blood by giving sod. bicarb. gr. xv a few days before operation. Ketosis, which is an important factor in post-anæsthetic toxæmia and acidosis, is decreased by giving a preliminary saline enema with 1 ounce of glucose and 1 ounce of olive oil. Olive oil is also useful as a rectal injection after operations, as it ensures the restoration of certain properties in the blood which are inhibited by the anæsthetic, e.g. phagocytosis, and it speedily restores the opsonic index.

* A paper read before the Sixteenth All-India Medical Conference at Lahore, 1939.

In a healthy patient who has been properly prepared and suitably premedicated, the administration of pure anæsthetic drugs should not cause toxic effects provided that the minimum quantity of anæsthetic compatible with satisfactory muscular relaxation is not exceeded. Overdose, even with the use of weak anæsthetics like N_2O, is harmful. To prevent overdose of any one particular anæsthetic agent, the method of *synergistic anæsthesia* is recommended, i.e. a combination of several hypnotic drugs which, according to Burg's law, causes a summation of effects and so results in a greatly enhanced narcotic effect than the mere use of one anæsthetic agent alone even in a large dose. With this object it is useful to adopt the following procedure for a strong adult who is to undergo a major abdominal operation. First give the patient a non-depressant hypnotic like veronal or phanodorm the evening before the operation. Inject morphia gr. 1/6 preferably dissolved in 2 c.c. of a 25 per cent. pure mag. sulph. solution and atropin gr. 1/100 one hour before the operation. In alcoholics and athletes, scopolamine gr. 1/100 is also added to it. Then half an hour before the operation give avertin *per rectum* in the proportion of 0.06 to 0.08 grms. per kilogram of the body weight of the patient in a 3 per cent. solution in aqua destil. Then make a field-block round the area of operation with a 0.5 to 1 per cent. novocain solution ten minutes before the incision. Then at the time of operation N_2O and O is administered, and if further complete relaxation of the abdominal parieties is called for a little ether or vinesthene or both are added.

This technique is advantageous because psychic shock is entirely eliminated, anoci-association is obtained, the toxic effects of inhalational anæsthetics are greatly reduced because only a small dose of inhalation anæsthetics is needed, and due to the synergistic action of several drugs an enhanced anæsthetic effect is produced with complete relaxation.

For *premedication*, morphia has several disadvantages as it sometimes causes complications, viz. respiratory depression, vomiting, troublesome constipation, abdominal distension, headache, and interference with kidney secretion. Hence, recently other drugs have replaced morphine for pre-medication: Omnopon gr. ⅙ to ⅓, nembutal gr. ½ to 1½, sodium soneryl gr. 2¼, dilaudid hydrochlor. gr. 1/32 to 1/12, preanest

0.5 to 1 c.c., etc. Dilaudid has a greater analgesic effect without any of the above-mentioned drawbacks of morphine, and it is now in vogue in America. Preanest, which is an Italian preparation, is in vogue in Europe and is by far the best and least toxic drug for premedication. The use of suitable premedication lessens the dose of inhalational anæsthetic, and so anæsthetic toxicity is decreased.

As regards avertin, its detoxication takes place in the liver, and elimination by the kidneys, hence in diseases of these organs avertin becomes highly toxic. The toxicity of avertin is somewhat neutralised by thyroxine or benzedrine. Avertin has a slight depressant effect on the respiratory centre and on the blood-pressure, but this is readily improved by CO_2 inhalations and cardiazol or coramine injection. Further observations of the use of avertin are given by me in the *British Journal of Anæsthesia*, October 1933.

To save the patient from the toxic effects and complications of anæsthetics, the planes of the different stages of anæsthesia should be skilfully regulated by deepening or lightening the anæsthesia as required. According to "the law of diminished resistance" the vitality of the patient is decreased as the anæsthesia progresses, and therefore the amount and percentage of an anæsthetic vapour must be also proportionately decreased, otherwise there may be great depression of the vasomotor and other centres with fall of blood-pressure. However, due to the many troublesome operative reflexes that may be set up during the operation, the *anæsthesia must be skilfully regulated* to avoid shock from the operative reflexes by deepening the plane of narcosis whenever necessary. These operative reflexes are brought about by prolonged and severe traction by retractors, tight packing of the abdominal cavity around the area of drainage, prolonged and undue elevation of the rest or bridge placed under the kidney or gall-bladder region, eversion of the liver, rough exploration, hæmorrhage, etc. These reflexes are harmful as the patient has to be kept deeply under for a long time, which necessarily causes depression of the vasomotor and other centres.

To lessen toxicity of inhalational anæsthetics, it is necessary that they should be quickly eliminated from the system.

Pulmonary ventilation should therefore be carried out, as soon as the operation is over, by the interrupted administration of CO_2 gas for a few minutes. This causes deep and rapid breathing and the anæsthetic is quickly blown away from the lungs. In cases where pulmonary complications are anticipated, due to prolonged deep anæsthesia in elderly patients, it is advisable to make the patient inhale carbogen, which is a mixture of 5 per cent. CO_2 and 95 per cent. oxygen, or CO_2 alone for a few minutes every hour after the operation for about 8 hours, and to ask the patient to cough frequently (for cough is really the watch-dog of the lungs), and also to get the patient turned from one side to the other every few hours. To safeguard against the occurrence of pneumonia, the use of heated anæsthetic vapours is recommended particularly on cold days. Shipway's apparatus is quite useful. Care should be taken that when the patient is removed from the heated theatre to his room he does not catch a chill in the escalator or through the cold corridors. Tight bandaging of the abdomen and over the lower ribs, intercostal paralysis after high spinal analgesia, conditions in which deep breathing or coughing gives pain to the patient, are apt to cause pneumonia and should be remedied. If pneumonia is developing, the use of M.B. 693 is indicated.

Proper selection of the anæsthetic and the method of its administration greatly decrease the risks of anæsthesia, whereas any fault or irregularity may become manifest by any one of the danger signs of anæsthesia as regards breathing, pulse, pupils, colour, etc. To prevent complications, the anæsthetist should never wait for all the classical signs of the fourth or toxic stage to be present, but should be able to understand the significance of any single abnormality that may arise during conduction of anæsthesia. Any error of judgment or lack of promptness in treating a complication is sometimes enough to send the patient off to the other world within a couple of minutes. Hence, the following brief practical points may prove valuable:

1. Apnœa, or transient cessation of breathing, should be interpreted as due to acapnia—i.e., deficiency of CO_2 tension in the blood.

2. Dyspnœa, or difficult breathing, points to some partial obstruction in the air-passages.

3. Dusky colour or cyanosis points to anoxæmia.

4. Quick and deep breathing means excess of CO_2 tension in the blood.

5. Quick and small pulse with low pressure indicates shock, vasomotor paralysis, and depressed circulation.

6. Dilated and inactive pupils speak of the patient entering the fourth or toxic stage.

7. Bradycardia and low tension speak of a *hyperactive carotid reflex*.

It has recently been shown that the carotid body, which is located at the bifurcation of the common carotid artery, is affected by changes in the chemical composition of blood by anæsthetic agents, by pressure on the neck over its region, etc., and these causes of stimulation of the carotid body set up certain harmful reflexes causing syncope, bradycardia, and hypotension during operations. This can be remedied by injecting 1 per cent. novocain solution in the region of the carotid body, on one or both sides of the neck. A hyperactive carotid reflex can be diagnosed easily previous to operation by the occurrence of the characteristic syndrome, viz. syncope, bradycardia and hypotension on pressure with the fingers, for a couple of minutes, over the carotid body with the patient in a standing or sitting position. In such cases a prophylactic injection of 1 per cent. novocain in the region of the carotid body on both sides of the neck is indicated before operation.

Now there are some other signs and problems of anæsthesia which if wrongly interpreted may cause unnecessary complications and even prove disastrous. For instance, jactitations or spasmodic movements of the fingers which are known as piano-playing movements and tremors, or twitchings, are a sign of anoxæmia and not a sign of the patient coming out of anæsthesia before the corneal reflex is absent. Sometimes an inexperienced surgeon seeing these jactitations believes that the patient is coming out of anæsthesia and wrongly asks the anæsthetist to deepen the anæsthesia, sometimes with disastrous results. Also apnœa, or transient stoppage of breathing during operation, is sometimes mistaken even by an

experienced surgeon to be due to overdose although there is no cyanosis. Apnœa is really due to acapnia, and the administration of CO_2 at once re-starts the breathing, whereas oxygen and artificial respiration are useless in this condition as they delete more CO_2 from the system. If there is no CO_2 cylinder available, the anæsthetist should keep the mask on the patient's face to promote re-breathing, and after taking a deep inspiration he should hold his breath and then blow out his own CO_2 into the patient's throat, and at the same time should pull out the tongue, open the mouth and press on the chest.

Among the recent new inhalational anæsthetics, "Cyclopropane" and "Novanest" are considered to have very little toxicity. Cyclopropane is trimethylene, and is a hydrocarbon gas and is administered with a high percentage of oxygen. It is much in vogue in America and in England. "Novanest" is used in Italy and other parts of Europe.

As regards chloroform, it is so highly toxic that electrocardiograms always show much more toxic effects with it than any other anæsthetic. In a prolonged case chloroform may cause a certain amount of destruction of the red blood-corpuscles, poikilocytes, fatty degeneration of the heart, liver, kidneys, acidosis, arrhythmia, extra-systoles, ventricular fibrillation, hypotension, and heart failure. Chloroform vapour should always be diluted with 98 per cent. air during administration.

If oxygen is used, the tube should be attached separately under the mask, and oxygen should not be continuously bubbled through chloroform for a long time because phosgene gas, which is highly toxic, is liable to be formed, and may cause sudden death. Adrenalin injections are dangerous and must be avoided during chloroform anæsthesia, as ventricular fibrillation often occurs. Excessive adrenalin is also produced in the patient's system during a prolonged and exhausting operation as a defensive action against the operative or histamine shock, and the excess of autogenous adrenalin sometimes sets up fatal ventricular fibrillation in chloroform anæsthesia.

A correct interpretation of the *Ophthalmic signs of Anæsthesia*, and the effects on the pupils of morphia or atropine, or both, will prevent unnecessary complications. The follow-

ing facts are worth remembering: Synechiæ or adhesions of iris do not let the pupils dilate, and even with dangerous overdose the pupils remain contracted. In some conditions the corneal sensibility to touch is lost or reduced as in absolute glaucoma, keratitis neuroparalytica, herpes, and in infants. The pupils remain dilated in cases of optic atrophy, glaucoma, and high myopia, contusions of the eye, after diphtheria, herpes, and in amblyopia. A coloboma of the iris, or wide iridectomy is sometimes mistaken for dilated pupils. Even artificial eyes are often not diagnosed, and I have seen students and doctors trying to elicit corneal reflex and reaction of the pupils in a glass eye. Hence, I may reiterate what I published in the *Practitioner*, of London, May 1932, that just as the heart and urine are examined before administration of anæsthesia, so the anæsthetist should inspect both the eyes as a routine to avoid being misled later on.

As regards ethyl ether, to make it less toxic in a prolonged case a gentle stream of oxygen should be allowed to bubble continuously through the ether. It should be remembered that ether causes suppression of urinary secretion for several hours after the patient is fully under, and hence in nephrectomy cases if there is hypofunction of the remaining kidney, the patient may die from anuria. Ether is also toxic in old, chesty people with sclerotic kidneys and high blood-pressure, and so ought to be avoided in them. By the open method in summer I have seen more than 1 lb. of ether being used for one case by beginners, so that complications are frequent. But the skill of the anæsthetist lies in using a minimum amount of anæsthetic compatible with adequate relaxation. With this object, I have devised a mask which is known as *Double Mask*, and is economic as it prevents wastage of ether. An account of it is published in the *Medical Annual*, 1936, and in the *British Journal of Anæsthesia*, October 1939.

Sometimes during prolonged open ether, or ether-and-oxygen anæsthesia, undesirable complications occur, e.g. irregularity in breathing, apnœa due to acapnia, ether convulsions, etc. These are generally obviated if a minimum amount of ether is used and CO_2 tension is uniformly maintained in the blood. With this object I have devised a special form of ether called *Carbonised Ether*, which is ethyl ether previously treated

with CO_2 gas. The advantages of this carbonised ether are that as the respiratory centre is gently stimulated, the breathing remains uniformly deep, the induction stage is quickened, and a less amount of ether is sufficient for keeping the patient well under with adequate relaxation. Hence, as less ether is used, the toxic effects of ether are reduced. In addition to these advantages, as the CO_2 tension is maintained shock is lessened, and it also counteracts the depressant effects on the respiratory centre of preliminary morphia and avertin if given to the patient before the general anæsthesia. This carbonised ether is made for me and is obtainable from Messrs. Howards, of London, and Duncan Flockhart & Co., of London and Edinburgh, and also from ether manufacturers in India. Further particulars about it are published in the *British Journal of Anæsthesia*, April 1938.

For the prophylaxis and cure of any type of dyspnœa, stridor, laryngospasm, and atelectasis or massive collapse of the lung, after removing any mechanical obstruction and after swabbing the throat and removing any tenacious mucus with a suction apparatus, the administration of helium gas has recently come into vogue. With the use of helium alone or helium combined with oxygen, there is less exertion to the patient during respiration, and so dyspnœa soon gives way to easy breathing. Even for the medical treatment of patients suffering from emphysema, bronchiectasis, pulmonary fibrosis or severe asthma, a mixture of helium and oxygen is nowadays employed by some physicians. Helium is an inert gas, is very light, and has a rapid rate of diffusion. It has been proved that there is deprivation of inert gases in the lungs during inhalational anæsthesia which causes atelectasis. Normally the nitrogen of the air supplies the necessary inert gas. As the usual anæsthetic gases which are inhaled are rapidly absorbable, it is advisable to safeguard the disaster of atelectasis by the administration of helium along with the anæsthetic vapours.

As regards *Spinal Anæsthesia* its toxicity and danger is great if the blood-pressure is allowed to fall and if the level of analgesia rises above the nipple line. The following are some means for reducing the dangers of spinal anæsthesia:

1. The use of hypobaric solutions (i.e., solutions lighter

than the specific gravity of the cerebro-spinal fluid); e.g., percaine 1 in 1500, 15 to 20 c.c., or novocain 4 per cent., 2 to 3 c.c. Personally, I prefer novocain.

2. The injection of these light solutions should be with the patient lying in the lateral flexed position rather than the sitting position.

3. The table should be immediately tilted in Trendelenburg position when light solutions are used, and the head is kept low during and several hours after the operation to prevent secondary fall of blood-pressure.

4. Reliable vaso-constrictors should be injected just after the spinal injection. Ephedrine, veritol, and neo-synephrine hydrochlor. are effective vaso-constrictors.

As regards *Intravenous Anæsthesia*, pentothal sodium is so far the best drug. The toxic effects of intravenous anæsthesia are manifested by the occurrence of pallor and not cyanosis, nervousness, quick and small pulse with low tension, sweating, fainting, nausea, tremors, convulsions, and death. To minimise their toxic effects, injections should be given slowly. If the anæsthesia wears off before the operation is over, ether, etc., should be given. In liver diseases, heart and respiratory diseases, quinsey, in low blood-pressure intravenous drugs should be avoided. To eliminate the toxic effects and quickly revive the patient from circulatory and respiratory depression, inject as a routine a reliable analeptic as soon as the operation is over. Coramine, cardiazol, neo-synephrine hydrochlor. and veritol are good analeptics.

ABSTRACTS

"Anæsthesia for Upper Abdominal Operations." C. C. STEWART in *Canadian Med. Journ.*, March 1940, p. 255.

ALTHOUGH there is nothing new in it this is an admirable exposition of its subject. The author favours endotracheal administration and believes that ether should be the most commonly employed agent although he approves of cyclopropane in the hands of those skilled in its use; he also admits the value of spinal anæsthesia by pontocaine glucose solution or nupercaine by the Howard-Jones or Etherington-Wilson techniques. He rules out avertin for gastro-intestinal and gall-bladder surgery and considers nembutal an uncertain drug. He finds that he has been unable to modify the more serious pulmonary post-operative infections by any one method.

Aetiology of "Ether Convulsion." L. H. MONSEL in *Proceedings of Mayo Clinic Staff*, June 1940.

THE author refers to the work of Rosenow and Tovell who discovered a neurotropic strain of streptococcus in five patients who underwent convulsions during anæsthesia. They suggested that "ether convulsions are attributable to a neurotoxin produced by some strains of streptococci in amounts insufficient to cause spasms in the absence of anæsthesia but which in the course of general anæsthesia suffice to incite the muscular spasms characteristic of ether convulsions". The case of a child of six is then related. She underwent a plastic operation under nitrous oxide, oxygen and ether. At the end of it, after anæsthesia had become light, twitchings were noticed around the eyes. They spread to face, neck, and trunk and convulsions soon became severe, the pulse rapid, the pupils dilated, and the face cyanosed. Six c.c. of 2.5 per cent. pentothal were injected by vein and oxygen administered. Convulsions quickly ceased and cyanosis disappeared. The concentration of blood-

calcium immediately following the convulsions was 9.5 m.g. per 100 c.c. Cultures made from nasal pharyngeal swabbings showed growth of a neurotropic strain of streptococcus. Her temperature was normal the day after operation and convalescence uneventful.

Cerebral Complications after Operation. A. Behrend and Helena E. Riggs in *Archives of Surgery*, January 1940, p. 24.

Post-operative cerebral embolism, which is often cited as the cause of symptoms, is extremely uncommon. Cerebral symptoms, however, are not uncommon after operation and the authors have studied 21 cases from one large hospital. Preoperatively only six of the patients could be considered poor surgical or anæsthetic risks. The average age was 38 years, and only four patients were over 50. The operations were not all severe, indeed one was merely incision of a paronychia. The anæsthetics concerned were: Ether (12), cyclopropane (4), nitrous oxide (3) and novocain for spinal analgesia (2). The phenomena noted were: Death during operation (3), psychic disturbances (3), prolonged coma (5), general convulsions (5), focal cerebral symptoms (paralysis) (5). Four of the patients with focal cerebral symptoms were under 33 years of age; the fifth had shown transient weakness of the right side for nine days before operation, complete paralysis developing within 24 hours after. Convulsions and coma may be observed while the patient is in the operating theatre. Psychotic manifestations may become apparent within a few hours after return of consciousness, or may not be noticed for several days. Fourteen of the patients who survived longer than twelve hours died with hyperpyrexia unexplainable by infection. Gross inspection of the brain lent no support to the theory of infarction as a result of embolism. Histologically the authors confirmed Courville's theory of widespread cellular degeneration throughout the brain. In every case there was generalised capillary damage with parenchymatous degeneration due to pericellular and interstitial œdema. The degeneration was most marked in the association areas of the cortex, sympethetic ganglia in the grey matter around the third and

fourth ventricles and lenticular nucleus, the dentate and Purkinje's cells of the cerebellum and the region of the inferior olive in the medulla. These are the areas that Chornyak has found most severely affected in animals subjected to atmospheres deficient in oxygen. The authors state that though they have been "able to demonstrate that death following anæsthesia is the result of a generalised circulatory insufficiency in which cerebral symptoms dominate the picture, it has not been established whether the anæsthetic is the causative agent or merely the precipitating factor." The lesions were essentially the same whatever the anæsthetic. Examination of the brain and other viscera reveals that cardio-circulatory efficiency usually has been impaired long before the operation. This is manifested by parenchymatous oedema and congestion and by perivascular fibrosis. The presence of diminished circulatory efficiency is generally unsuspected. To sum up, cerebral complications after operation are frequently the sequel to relative cerebral anoxia produced by alteration in blood-pressure occurring as the result of operation and of anæsthetic in a patient with impaired cardio-circulatory efficiency.

"Benzedrine Sulphate to Interrupt Avertin Anæsthesia." John Boyd in *B.M.J.*, May 4, 1940, p. 729.

The author gives a *résumé* of previous experiences which other observers have had with other drugs designed to cut short anæsthesia from avertin. Animal experiments with benzedrine sulphate were encouraging and it was tried satisfactorily on human beings. Boyd reports on its use on twelve children given a relatively large dose of avertin. His conclusions are that the immediate effect of the injection of benzedrine sulphate is return of superficial reflexes. The post-operative sleep is reduced, and most of the patients vomited profusely

"Views on Avertin." *Canadian Med. Assoc. Journ.*, December 1939, p. 609.

It is the opinion of Dr. Wesley Bourne that *the* specific antidote for avertin overdosage is ephedrine sulphate gr. ¾ to 1½

given intramuscularly, or intravenously if the condition is alarming. In the experience of others also this treatment has been superior in all respects to coramine, metrazoy, caffeine, sodium benzoate, etc., which have been recommended for use when respiration or circulation fails after avertin injection.

"*A Newer Anæsthetic; Ethyl N. Propyl Ether.*" W. E. Brown in *Canadian Med. Assoc. Journ.*, April 1940, p. 310.

This article describes a purely experimental study involving certainly inhalation of the new anæsthetic by a human being but otherwise confined to animal experiments. The result of both these and of the human experience suggest that the new ether deserves further trial even in the operating theatre. As far as the experiments go it has been shown to be easily inhaled and remarkably free from deleterious influence on blood-pressure or pulse-rate as well as giving quick recovery without sickness. It is made by the action of ethyl iodide upon sodium N. propylate in an excess of alcohol which is afterwards distilled off.

"*Cyclopropane—Unmixed.*" B. C. Leech and H. G. Griffith in *Canadian Med. Assoc. Journ.*, May 1940, p. 435.

This article contains most important clinical evidence of the value of cyclopropane as an anæsthetic *per se*. The authors' combined experience covers more than eight thousand administrations—the only fatalities, of which details are given—were obviously not mainly, if at all, due to cyclopropane. Over three thousand of the operations concerned were abdominal. The authors state that "any demanded depth of anæsthesia can be produced more safely with cyclopropane than by any comparable agent or method." They see no reason for not beginning with cyclopropane since induction is pleasant, rapid and rarely accompanied by excitement or struggling. Cardiac arrhythmia is common, but is quickly removed by additional oxygen. The authors have had no trouble at all from explosion or fire. They have always used closed CO_2 absorption apparatus, and often employed the endotracheal method.

OBITUARY

Herbert Charles, M.R.C.S., D.A.

HERBERT CHARLES, who died on January 13th last, lived through revolutionary changes in methods of anæsthesia, the nature of surgical operations and the status of anæsthetists. Qualifying in 1906, he became house-surgeon to the late Sir John Bland Sutton, after which for thirty-odd years he held successively the appointments of assistant anæsthetist (1907), honorary anæsthetist and consulting anæsthetist (1931) to the Middlesex Hospital. He was the first anæsthetist appointed to the Royal Masonic Hospital when that institution was founded, continuing in its active service to within three weeks of his death —some eight years after retiring from the active list at the Middlesex Hospital.

When first appointed to the staff of the Middlesex Hospital it was his duty to turn up at 5 p.m. each operating day to relieve his seniors, if they so desired. A bagful of N_2O as an introduction to "the Clover" and a switch-over to chloroform if the operation exceeded some thirty minutes or the patient was "getting too moist" filled the bill in most cases. The Junker and a flexible mouth-tube did duty for most fancy work. The advent of open ether caused quite a stir!

At this time the surgical attitude towards the anæsthetist was one of toleration for a necessary supernumerary, and perhaps, in consequence, there was not so much competition for the post. Yet Charles lived to see anæsthetists accepted as equal colleagues on the Medical Committee.

As an anæsthetist, Charles' technical ability, clinical instinct and ideal temperament have been vouched for by surgical colleagues in recent numbers of the *Lancet* and *British Medical Journal*.

"Never ruffled or flurried or uncertain, whatever the surprise or emergency, and steady as a rock under all conditions." Thus

writes Mr. Victor Bonney, after working with Charles more than with any other anæsthetist. To anæsthetise between 500 and 600 patients for Wertheim's operation without a single death on the table speaks for itself.

Charles was a practical rather than a scientific anæsthetist, and always avoided complicated apparatus and technique when, in his opinion, the simple methods would do as well.

Of a bright and breezy temperament, Charles could always adapt himself to the occasion. To the frightened patient his kindly and inspiring presence and ready sympathy and understanding never failed to win confidence. " He always seemed more like a friend than a doctor."

To students he imparted a real interest in anæsthetic work, and he had reduced teaching to a fine art—partly because he could bring himself down to their level, and partly because he was content to deal with practical essentials only. A one-time student recalls how that he always gave a better anæsthesia for Charles than any of the other anæsthetists. Charles gave him confidence and did not worry him. Yet again, a now well-established surgeon considers that Charles was more encouraging to the young surgeon than any man he ever worked with, offering a helpful hint at the right moment without in any way appearing to interfere.

Charles spent his leisure in varied ways. In his early days his virile and athletic nature found an outlet in cycle-racing and, for a time, he held the world's record for twelve and twenty-four hour tandem-riding on the road. At other times he would make excursions to the New Forest to collect butterflies. Later in life he became a keen golfer, and was captain of Kingsdown. In conversation, Charles always seemed able to speak with the authority of an expert—and he was seldom proved wrong, no matter what the topic.

Charles will be remembered with affection by all anæsthetists of " the old school " as a loyal and lovable colleague and a man whose excellent work helped to lay the solid foundation upon which present advances have been built.

CORRESPONDENCE

Copy of letter from EVERETT A. TYLER, M.D., 1113 Medical Arts Building, Philadelphia, to A. CHARLES KING, Ltd., 34 Devonshire Street, Harley Street, W.1.

February 12, 1940

Gentlemen,—In view of the fact that there is considerable discrepancy in the sizes of catheters for anæsthetic purposes, as at present marked with the numerals 00 to 10, the American Society of Anæsthetists believe that it would be advisable to have all catheters for anæsthetic purposes marked according to a standard scale.

The United States Government has promulgated certain requirements for the use of soft rubber catheters and specified that they shall be marked according to the French scale. The members of the American Society of Anæsthetists feel that it would be advisable to follow this plan and request manufacturers to so mark catheters for endotracheal anæsthesia.

May we solicit your co-operation and ask that you mark all catheters for endotracheal anæsthesia according to the French scale?

Thanking you for your co-operation and for any suggestions that you may care to make, I am, yours very truly,

(*Signed*) EVERETT A. TYLER

Chairman Research Committee, American Society of Anæsthetists.